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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/726,236	LOCKRIDGE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) 9 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 and 10-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 02 December 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/14/05 & 12/2/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26 are pending in the instant application.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Claims 1, 8, and 9 are subject to a restriction since it is not considered to be a proper genus/Markush. See MPEP 803.02- PRACTICE RE MARKUSH-TYPE CLAIMS - If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction. Since the decisions in re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

Claim 1 specifically claims a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of VEGF or a VEGF

receptor. Claims 8 and 9 depend on claim 1 and add the further limitations wherein the VEGF receptor is VEGFR1 and VEGFR2, respectively. VEGF and VEGF receptor are each independent genes, which are structurally and functionally independent and distinct for the following reasons: Each gene has a unique nucleotide sequence which is structurally and functionally independent, each from the other. As such the Markush/genus of methods of locally administering a double-stranded RNA complementary to a nucleotide sequence of VEGF or a VEGF receptor are not considered to constitute a proper genus, and is therefore subject to restriction. Furthermore, a search of more than one (1) of the methods of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of VEGF or a VEGF receptor as claimed in claim 1 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed independent genes. In view of the foregoing, one gene selected from VEGF or a VEGF receptor is considered to be a reasonable number of sequences for examination. Accordingly, applicants are required to elect one gene selected from the method of locally administering a double-stranded RNA complementary to a nucleotide sequence of VEGF or a VEGF receptor from claim 1. If Applicants elect a method of locally administering a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor, a further restriction is required between VEGFR1 and VEGFR2 as recited in claims 8 and 9, respectively. Note that this is not a species election.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Claims 2-7 and 10-26 links the inventions of claim 1. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

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In a telephonic conversation with Anita Terpstra on March 8, 2006, a provisional election was made with traverse to prosecute a method of locally administering a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor from claim 1, and VEGFR1 from claim 8. Affirmation of this election must be made by Applicant in replying to the Office Action.

Applicant is reminded that claim 1 links the invention of claims 2-7 and 10-26 and

will be examined with the elected invention. The restriction requirement among the linked invention is subject to the nonallowance of the linking claim, claim 1.

Applicant is also reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim 9 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) in the conversation on March 8, 2006.

Claims 1-8 and 10-26 have been examined on the merits.

Information Disclosure Statement

The information disclosure statement filed October 14, 2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

The information disclosure statement filed December 2, 2003 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith. However, referring to Reference No. 45, JP 08208687, filed

August 1996, only the Abstract has been considered for this reference since it is a Japanese patent and Applicants have only provided an English translation of the Abstract.

Priority

It is noted that the instant application is a continuation-in-part of USSN 10/306,747 filed November 27, 2002, which claims benefit of U.S. Provisional Application No. 60/334,461, filed November 30, 2001, U.S. Provisional Application No. 60/358,580 filed February 20, 2002, U.S. Provisional Application No. 60/363,124, filed March 11, 2002, and U.S. Provisional Application No. 60/393,796, filed July 3, 2002, which is a continuation-in-part of International Application No. PCT/US02/17674, filed May 29, 2002; which is a continuation-in-part of USSN 10/138,674, filed May 29, 2002; which is a continuation-in-part of USSN 09/870,161, filed May 29, 2001; which is a continuation-in-part of USSN 09/708,690, filed November 7, 2000; which is a continuation-in-part of USSN 09/371,772, filed August 10, 1999; which is a continuation-in-part of USSN 08/858,040, filed January 11, 1996; which claims the benefit of U.S. Provisional Application No. 60/005,974 filed October 26, 1995.

The instant claims are drawn to a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor. It is noted that the instant specification at page 21, last paragraph discloses, "The term "double-stranded RNA" or "dsRNA" as used herein refers to a double-stranded RNA molecule capable of RNA interference "RNAi", including short interfering

RNA "siRNA"". When reviewing the parent applications for support, the terms "RNA interference" or "RNAi" are only found in U.S. Provisional Application No. 60/334,461, filed November 30, 2001.

In summary, the claimed invention has been afforded priority to U.S. Provisional Application No. 60/334,461, filed November 30, 2001 because no other parent application(s) for which Applicants claim benefit have support for the terms "RNA interference" or "RNAi".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite because the term "VEGFR1" is not clearly defined. Since abbreviations often have more than one meaning, it is suggested that inserting the full name of the growth factor receptor would overcome the instant rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 10-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-8 and 10-26 are drawn to a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor. It is noted that the instant specification at page 21, last paragraph discloses, "The term "double-stranded RNA" or "dsRNA" as used herein refers to a double-stranded RNA molecule capable of RNA interference "RNAi", including short interfering RNA "siRNA"".

The specification discloses the pharmacokinetics and tolerability of an antiangiogenic VEGFR1 ribozyme, ANGIOZYME™, in a Phase I/II trial (see Figure 5 and Example 5).

The first issue is that the specification does not teach a single double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor. The disclosure of not a single species of a double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor provides insufficient written description to support the genus encompassed by the claim. Without a disclosure of a

single species of the genus, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecule(s). The lack of a singly disclosed species is not representative of the genus because the genus is highly variant (e.g. nucleic acid sequence).

The second issue is that the invention encompasses nucleic acids that encode all forms of a VEGF receptor(s), which includes mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology) and so forth. It is noted that the instant specification teaches a specific VEGF receptor, VEGFR1, also known as flt-1 (see the instant specification at page 4, first paragraph). The specification also discloses an antiangiogenic VEGFR1 ribozyme, ANGIOZYME™, that modulates the expression of human VEGFR1, GenBank Accession No. NM_002019. The art teaches VEGFR1/flt-1 from many different mammalian species with many different sequences. For example, the art teaches VEGFR1/flt-1 mRNA (GenBank Accession No. NM_010228); (GenBank Accession No. NM_019306); (GenBank Accession No. AF473823); (GenBank Accession No. AF063657); (GenBank Accession No. BC029674); (GenBank Accession No. AY404032); (GenBank Accession No. AY404031); and (GenBank Accession No. AY404033). There is no disclosure found in the specification or known in the art, at the time the instant invention was made that relates the structure of a double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor as claimed in the instant invention. The claims are directed to encompass a broad range of double-stranded RNA molecule(s) capable of RNA

interference that is complementary to a nucleic acid molecule encoding a VEGF receptor, of highly variant structures (e.g. nucleic acid sequence), which have not been described in the specification and whose structure could not be envisioned by the skilled artisan based on the disclosure of the specification.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or

simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a single species of a double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor, which would allow one of skill in the art to predict the structures of all members of the claimed genus of VEGF receptor double-stranded molecules. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Without a single disclosed species, one of skill in the art, at the time the instant invention was made, could not envision any double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor, and therefore one of skill would not be convinced that applicants were in possession of any double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor that are heretofore undescribed. Therefore, the specification does not describe the claimed double-stranded VEGF receptor molecules for use in a method of locally administering to a cell or tissue in such full and concise terms so as to indicate that the applicant had possession of these nucleic acid

molecules at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

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Claims 1-8 and 10-26 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of locally administering to a cell or tissue *in vitro*, a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor, does not reasonably provide enablement for a method of locally administering to a cell or tissue *in vivo* (whole organism), a double-stranded RNA complementary to a nucleotide sequence of a VEGF receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

The instant claims are drawn to a method of locally administering to a cell or tissue a double-stranded RNA complementary to a nucleotide sequence of a VEGF

receptor. The broadness of the method recited in the instant claims implies *in vivo* applicability of this method for enablement purposes. It is noted that the instant specification at page 21, last paragraph discloses, "The term "double-stranded RNA" or "dsRNA" as used herein refers to a double-stranded RNA molecule capable of RNA interference "RNAi", including short interfering RNA "siRNA"".

The specification discloses the pharmacokinetics and tolerability of an antiangiogenic VEGFR1 ribozyme, ANGIOZYME™, in a Phase I/II trial (see Figure 5 and Example 5). The specification goes on to disclose that the ANGIOZYME™ interfered with the menstrual cycle of one of the patients in the Phase I/II trial, perhaps by inhibiting neovascularization of uterine tissue. Based on these results, the specification contemplates that ANGIOZYME™ and/or other nucleic acid inhibitors of gene expression could be used to treat female reproductive disorders and conditions, such as endometriosis (see page 6, first full paragraph).

The specification does not demonstrate any correlation with the administration of a VEGFR1 ribozyme (ANGIOZYME™) with the administration of a double-stranded RNA molecule capable of RNA interference (e.g. siRNA) *in vivo*. The specification does not present any examples wherein a double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor was delivered to cells *in vivo* (whole organism).

At the time the instant invention was made, the therapeutic use of double-stranded RNA molecules capable of RNA interference, including siRNA, was highly unpredictable due to obstacles that continue to hinder the therapeutic application of

oligonucleotide-based therapeutics *in vivo* (see for example Hannon et al., Nature, 2004 Vol. 431:371-378; Downward, J., BMJ, 2004 Vol. 328:1245-1428; and Paroo et al., Trends in Biotechnology, 2004 Vol. 22:390-394). Such obstacles include, for example, siRNA duplex stability, delivery, issues of absorption, distribution, metabolism, and excretion. Hannon et al. state, "It is feasible to infuse backbone-modified oligonucleotides *in vivo,* but achieving intracellular delivery at therapeutically effective concentrations is a major challenge. Targeted delivery to specific cell or tissues types is till not a practical reality for oligonucleotide-based therapeutics" (see page 377, second column, first full paragraph). Hannon et al. also state, "Despite considerable hurdles to overcome, it seems likely that RNAi will find a place alongside more conventional approaches in the treatment of diseases, although it is unclear how long we will have to wait to witness the first RNAi-based drug" (see page 377, second column, last paragraph).

Downward, J. outlines that RNA interference can be used as an effective therapeutic strategy, however considerable problems relating to delivery to target cells will have to be solved (see Abstract). Downward further addresses the unpredictability and the problems faced in the siRNA art with the following statements: "Although a big improvement on previous methods, RNA interference has its limitations. Not every sequence works – most researchers get a success rate of about one in three. In addition, although the effects are generally thought to be highly sequence specific, some question marks remain as to whether or not some of the effects seen are "off target"" (see page 1246, last paragraph). Downward adds, "RNA interference clearly

has much promise in the laboratory"... "However a huge gap exists between achieving results *in vitro* and in a whole animal or patient" (see page 1247, second column, first paragraph). Downward concludes with, "The major challenge in turning RNA interference into an effective therapeutic strategy is the delivery of the RNA interference agents... to the target cells within the body" (see page 1247, second column).

Paroo et al. address the unpredictability associated with siRNA therapy with the following statements: "In contrast to the great success of synthetic siRNA in mammalian cell culture, there have been few reports employing synthetic siRNA in animals. Developing siRNA for efficient gene silencing *in vivo* is likely to be more challenging and many issues must be addressed before use in animals can become routine". Paroo et al. also state, "Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

Given this unpredictability, the skilled artisan, at the time the instant invention was made, would require specific guidance to practice the method of delivery as claimed. The specification provides examples wherein an antiangiogenic VEGFR1 ribozyme, ANGIOZYME™, is delivered to patients in a Phase I/II trial. However, delivery of ribozyme nucleic acids *in vivo* are generally not predictive of delivery of double-stranded RNA molecules capable of RNA interference (e.g. siRNA) *in vivo* due to differences in the duplex nature of the double-stranded RNA molecule capable of RNA interference. Although double-stranded RNA molecule(s) capable of RNA interference, including siRNA, and traditional ribozyme/antisense oligonucleotides share

many features, there are also important differences between the two. For example, Paroo et al. states, "The main challenge for developing siRNA *in vivo* is delivering duplex RNA intact to a target tissue" (see page 393, first column). Paroo et al. also state, "The higher molecular weight of siRNA can also make uptake by cells more difficult. Furthermore, the presence of a second nucleic acid strand increases the potential for off-target effects. Because single-strand RNA is highly labile, maintaining hybridization of the duplex is essential for delivery of siRNA" (see page 393, first column). Paroo et al. conclude with, "Even with the great progress that has been made, it is not clear whether or not siRNA possesses any advantages relative to traditional antisense oligonucleotides for *in vivo* experiments or therapeutic development" (see page 393, last paragraph).

The field of double-stranded RNA molecule capable of RNA interference, such as siRNA therapy, at the time the instant invention was made and to date, does not provide guidelines by which siRNA molecules, for example, can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in methods of treatment as contemplated in the instant invention. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver a double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor to generally any target cell or tissue *in vivo* at a concentration effective to treat female reproductive disorders and conditions, such as endometriosis as contemplated.

In order to practice the invention claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of how to specifically deliver a double-stranded RNA molecule capable of RNA interference that is complementary to a nucleic acid molecule encoding a VEGF receptor to an organism *in vivo* (whole organism) at a concentration effective to result in treating female reproductive disorders and conditions, such as endometriosis as contemplated in the instant invention. Additionally, this undue experimentation would include the determination of how to maintain the siRNA duplex, for example *in vivo*, where the art has shown that this is a great challenge. Given the art-recognized unpredictability of the therapeutic application of double-stranded RNA molecule(s) capable of RNA interference *in vivo*, this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods claimed, the state of the art of oligonucleotide-based therapy, the level of unpredictability of *in vivo* (whole organism) methods of using double-stranded RNA molecule(s) capable of RNA interference, the lack of specific guidance for the *in vivo* application of double-stranded RNA molecule(s) capable of RNA interference, and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods claimed, commensurate in scope with these claims, without undue trial and error experimentation.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
March 10, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635